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Research paper

Genetic susceptibility to prosthetic joint infection following total joint arthroplasty: A systematic review

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ABSTRACT

Background: Prosthetic joint infection (PJI) is the most common cause of total joint arthroplasty failure and revision surgery. Genetic polymorphisms could be determinant factors for PJI.
Methods: We performed a systematic research of Medline, Pubmed, Embase, Cochrane Library, and Google Scholar, and identified 11 studies with 34 kinds of gene polymorphisms, were included in the synthesis.
Results: Our data suggest that the C allele and genotype C/C for MBL-550 SNP, genotype A/A for MBL-54 SNP and G allele for MBL-221 SNP increase the risk of PJI, while G allele and genotype G/G for MBL-550 SNP decrease the risk of PJI in Caucasian populations. Several other genes reported by single-center studies also contribute to the genetic susceptibility to septic PJI. No definitive conclusions could be achieved due to the small amount of data in the included studies.
Conclusion: Several genes contribute to the genetic susceptibility to PJI following total joint arthroplasty. Further studies will enhance the understanding of PJI, and may inform and direct early interventions.

1. Introduction

Total joint arthroplasty (TJA) is a very effective procedure that substantially improves the quality of life in patients with end-stage joint affections, including osteoarthritis and rheumatoid arthritis. It is now estimated that millions of patients worldwide have received total joint replacements annually. Prosthetic implants relieve symptoms and improve quality of life, but some of these benefits are time limited. Prosthetic joint infection (PJI) is a feared complication threatening of total joint replacement regardless of the site. Numerous risk factors contributing to PJI have been identified in epidemiological studies such as rheumatoid arthritis, diabetes mellitus, revision arthroplasty, higher individual risk scores for anesthesia, and wound complications including superficial infections (Jamsen et al., 2009; Pedersen et al., 2010). Despite careful management and preventative measures, PJI can exhibit in up to 1.7% of primary hip arthroplasties and 2.5% of primary knee arthroplasties, dependent on anatomical localization of the arthroplasty (Cataldo et al., 2010). Majority of PJI is tightly linked to intraoperative contamination of prosthesis implantation. It was repeatedly demonstrated that any medical implanted device impairs local innate host response facilitating development of infection (Klouche et al., 2010). PJI usually requires revision surgery and, apart from detrimental effects on patients, multiplies the overall cost of TJA in affected individuals (Mrazek et al., 2013). To diminish intraoperative microbial exposure and increase the likelihood that the host immune response together with antibiotics will tackle remaining bacterial load, rigorous preventative measures have been introduced into clinical practice (Jamsen et al., 2010).

To try to identify preventive measures, possible biophysical, physical and biological factors have been investigated. At present, it is thought that susceptibility to PJI results from a combination of environmental and genetic factors. Environmental factors such as type of bacteria (Hall-Stoodley et al., 2004), prosthesis (Lima et al., 2013), material (Malchau et al., 1993), BMI (Somayaji et al., 2013), age (Meehan et al., 2014), diabetes mellitus (Malinzak et al., 2009), operative time (Naranje et al., 2014), malnutrition (Lima et al., 2013), HIV infection at an advanced stage (Issa et al., 2013), presence of distant infectious foci (Gerometta et al., 2012), and antecedents of arthroscopy or infection in previous arthroplasty (Lima et al., 2013; Le et al., 2014) have been widely studied, and investigations on genetic factors may well give a newly answer to this issue. Interindividual variability in cytokine and protein production has been observed, and these variations are suspected to be genetically determined, most frequently via the effects

Abbreviations: PJI, Prosthetic joint infection; TJA, Total joint arthroplasty; OR, Odds ratio; CI, Confidence intervals; OPG, Osteoprotegerin; SNP, Single nucleotide polymorphism; MBL, Mannose-binding lectin; TLR, Toll-like receptor; VDR, Vitamin D receptor; CXCL-1, CXC chemokine-ligand-1; CXCR2, Chemokine C-X-C motif receptor 2; IL, Interleukin; TNF, Tumor necrosis factor; MMPs, Matrix metalloproteinases.

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of polymorphisms within regulatory regions of the corresponding genes. Accordingly, relevant functional polymorphisms in the cytokine, receptor and protein genes may be implicated in the pathogenesis of PJI for example via impairing the effector phase of the innate immune response (Danis et al., 1995; Del Buono et al., 2012). Genetic polymorphisms are genetic variations that are considered biologically normal and can be found in at least 1% of the population (Del Buono et al., 2012). These variations may influence protein transcription, expression of related factors, immunoreaction and contribute towards individual susceptibilities to certain pathological conditions (Goodman et al., 1992). To date, some studies (Malik et al., 2006, 2007a, 2007b; Osmon et al., 2008; El-Helou et al., 2011; Malik et al., 2012; Navratilova et al., 2012a, 2012b, 2014; Stahelova et al., 2012; Mrazek et al., 2013) focusing on the role of heritable factors in individual susceptibility to PJI had been published, including the mutation of proteins, receptors, intracellular mediators, cytokines and enzymes. In the present study, we therefore performed a systematic review to investigate whether or not the gene polymorphisms are associated with PJI.

2. Materials and methods

2.1. Search strategy

We performed a systematic research of Medline, Pubmed, Embase, Cochrane Library, and Google Scholar to identify published epidemiological studies through March 2014 that were related to gene polymorphisms and prosthetic joint infection. The medical subject headings and free-text words of "polymorphism", "SNP", "gene", "genetic", "arthroplasty", "joint replacement", "prosthesis", "infection" and "prosthetic joint infection" were combined for free research. No language or other restrictions were placed on the search. Full-texts were obtained if the abstracts did not allow us to include or exclude the studies. Furthermore, the reference lists of all the related papers were examined to identify any initially omitted studies.

2.2. Inclusion and exclusion criteria

To be eligible for inclusion in the present study, the following items were established: (1) observational studies that addressed patients with PJI and healthy controls with aseptic TJA; (2) studies that evaluated the association between gene polymorphisms and susceptibility to PJI; (3) studies had sufficient genetic frequency for extraction; (4) case–control, cross-sectional cohort and prospective cohort studies were included; and (5) studies in abstract form, which the full paper could not be acquired, were also included. Exclude strategies are followed: (1) studies on patients who were not experienced joint replacement surgery were excluded; (2) cadavers, literature reviews, technical notes, biomechanical reports, case reports, in vitro, studies on animals and instructional course were excluded; (3) studies carried out on patients, who were pregnant, with cancer or other diseases were excluded; (4) overlapping study populations, interim analyses and comparisons of laboratory methods were excluded. Any publications with questionable were discussed and disagreements were resolved by consensus.

2.3. Study selection

Four reviewers independently screened the titles and abstracts. When there was uncertainty about any of the above vital information, the full article was retrieved for further scrutiny, or the authors of individual trials were contacted directly to provide further information when necessary. Subsequently, the literature was further reviewed to determine the final inclusion. Two of the reviewers independently evaluated the methodological quality of the included studies by

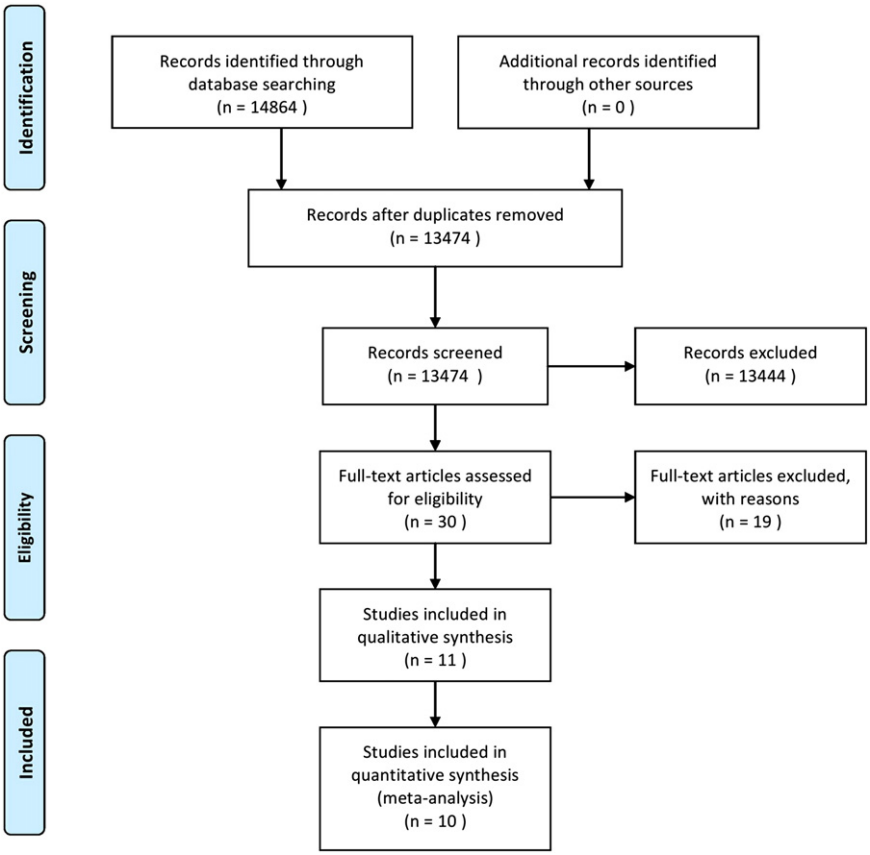

Fig. 1. A flowchart shows the results of the literature search and selection for this study.